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Factors associated with fibro-cavernous tuberculosis

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Abstract

Objective: To identify socio-demographic, clinical and laboratory risk factors associated with fibro-cavernous tuberculosis.

Material and methods: Clinical and laboratory data of 184 patients with pulmonary tuberculosis who were treated at the National Scientific Center for Phthisiopulmonology of the Ministry of Healthcare of the Republic of Kazakhstan were analyzed. Specific antibodies to the lipoglycan of M.tuberculosis (MBT) were evaluated in an immunochromatographic assay. To assess the significance of differences in groups, the Pearson Chi-Square test was used. To determine factors associated with the fibro-cavernous tuberculosis, a multiple binary logistic regression analysis was carried out.

Results: Multivariate logistic regression analysis showed that low BMI (OR=5,719, 95% CI: 2,049–15,965, p=0,001), TB recurrence (OR=3.374, 95% CI: 1,191–9,561, p=0,022), and a negative specific production of antibodies to lipoglycan of M.tuberculosis (MBT) (OR=0,354, 95% CI: 0,126-0,995, p=0,049) were significantly associated with fibro-cavernous tuberculosis.

Conclusion: Weight deficiency, high antibodies levels and TB relapse are factors associated with fibro-cavernous tuberculosis.

Key words: infiltrative tuberculosis, fibro-cavernous tuberculosis, risk factors, anti-tuberculosis antibodies

Introduction

Tuberculosis (TB) caused approximately 1.2 million deaths in 2019 and is one of the leading causes of morbidity and mortality worldwide [1].

At the same time, the formation of a destructive cavity in the lungs is an unfavorable stage in the course and outcome of the disease. Fibro-cavernous tuberculosis (FCT) and complications arising from it, in 75-80% of cases are the cause of death of TB patients [2].

The formation of a cavitary focus of disintegration of specific inflammation in the lungs can occur with the progression of any form of tuberculosis against the background of predisposing conditions, and is associated with treatment failure, which is manifested, among other factors, by delayed conversion of sputum culture, the relapse development and drug resistance [3]. According to data from various sources, the proportion of tuberculosis patients with cavitary foci in the lungs at the time of diagnosis ranges from 29% to 87% [4].

Studies conducted to date show that low weight, diabetes mellitus, history of alcohol abuse and smoking, and a positive cytology result are associated with fibro-cavernous tuberculosis [5].

However, the number of studies devoted to the analysis of factors associated with fibro-cavernous tuberculosis is limited. In this regard, further search for factors associated with this TB form is necessary, which will contribute to a clearer understanding of the pathogenesis of FCT and to ensure proper control of the relevant factors in the management of patients with tuberculosis.

Objective: To identify socio-demographic and clinical laboratory factors associated with fibro-cavernous form of tuberculosis.

Material and methods

Study population

Clinical and laboratory data of 184 patients with pulmonary tuberculosis who were treated at the National

Scientific Center for Phthisiopulmology of the Ministry of Healthcare of the Republic of Kazakhstan were analyzed. The diagnosis of tuberculosis was confirmed by molecular genetic (GeneXpert/Hain-test) and/or bacteriological (BACTEC) methods. All studies were reviewed and approved by the Local Ethics Committee of the Kazakh National Medical University.

The study population is presented in Table 1.

Table 1 Characteristics of TB patients

Parameters		Pulmonary TB N (%)
Total		184
Gender, n (%)	Male	117 (63,6%)
	Female	67 (36,4%)
Age (M+/-m, лет) 37,80±1,05	Up to 40 years old	113 (61,4%)
	Over 40 years old	71 (38,6%)
BMI, n (%)	Normal	148 (80,4%)
	Deficient	36 (19,6%)
Residence	City	120 (65,2%)
	Suburb	64 (34,8%)
Job	In work	43 (23,4%)
	Unemployed	141 (76,6%)
Income	Above the living wage (LW) *	64 (34,8%)
	Below the living wage (LW)	120 (65,2%)
TB contact	Yes	35 (19%)
	No	149 (81%)
HIV status	Postive	11 (6%)
	Negative	173 (94%)
Comorbidities **	No	124 (67,4%)
	Yes	60 (32,6%)
	1 disease	41 (68,3%)
	2 or 3 diseases	17 (28,3%)
	more than 3 diseases	2 (3,4%)
Microscopy n (%)	+1 +2 +3	63 (34,2%)
	Negative	121 (65,8%)
Molecular genetic technique, n (%)	Hain-test and/or G-Xpert***	169 (91,8%)
	Not conducted	15 (8,2%)
Bacteriological technique, n (%)	BACTEK и/или LJ****	134 (72,8%)
	Not conducted	50 (27,2%)
Drug sensitivity, n (%)	Drug sensitive	46 (25%)
	Drug resistant	
(MDR and/or XDR*****)	138 (75%)	
TB type, n (%)	New case	102 (55,4%)
	Relapse	82 (44,6%)
TB form, n (%)	Infiltrative	113 (61,4%)
	Fibrous-cavernous	36 (19,6%)
	Other forms ******	35 (19%)
Duration of current treatment, n (%)	From 1 to 6 months	141 (76,6%)
	From 6 to 12 months	30 (16,3%)
	>1 year	13 (7,1%)

* living wage for 2018

** Concomitant diseases included the following diseases: allergic dermatitis, hepatitis, anemia, bronchial asthma, diabetes mellitus, chronic alcoholism, chronic cholecystitis, chronic obstructive pulmonary disease, chronic pyelonephritis, Crohn's disease, coronary heart disease, hearing loss, salpingo-oophoritis, scleroderma, rheumatoid arthritis

*** Hain-test/G-Xpert – molecular genetic methods for diagnosing tuberculosis

**** BACTEK/LJ – bacteriological methods for diagnosing tuberculosis

***** MDR/XDR – multidrug resistance/extensive drug resistance

****** Other forms include the following forms of TB: caseous pneumonia, empyema, pleurisy, generalized, disseminated tuberculosis, tuberculoma

In 91.8% of patients the diagnosis was confirmed by Hain-test and/or G-Xpert, in 72.8% the diagnosis was also confirmed bacteriologically. At the same time, only in 34.2% of patients the diagnosis was confirmed by microscopy.

In the study group, there were almost 2 times more males than females (63.6% versus 34.4%, respectively). Moreover, 61.4% were patients under the age of 40 years. Almost one fifth of the patients were underweight. With regard to socio-economic status, 76.6% of TB patients were unemployed, and the number of patients with income below the subsistence level was 65.2%. Almost all patients (94%) were HIV negative. Only 19% of patients were able to indicate the presence of TB contact. With regard to the presence of comorbidities, 67.4% of patients had no history of comorbidities, and 32.6% of patients had various comorbidities. Of these, 68.3% of patients had a history of one disease, 28.3% had 2 or 3 diseases, and 3.4% had more than 3 diseases.

As for the TB characteristics, patients with drug-resistant TB prevailed among patients (75%), almost half of the cases (46.6%) were relapses of the disease, while the infiltrative TB prevailed (61.4%). The period from 1 to 6 months of treatment accounted for 76.6% of cases.

Immunochromatographic analysis

To determine specific antibodies to the lipoglycan of M.tuberculosis (MBT), immunochromatographic analysis was performed on the LioDetect TB-ST platform (Lionex GmbH, Germany).

Statistical methods

The obtained data were analyzed using the Microsoft SPSS 23.0 software package. To assess the significance of differences in groups, the Pearson Chi-Square test was used. To determine the factors associated with FCT, a logistic regression analysis was performed in univariable and multivariable models, where unadjusted and adjusted odds ratios (OR), as well as 95% confidence intervals were calculated. In the multivariable model, we included all variables regardless of the p-values identified in the univariable analysis. At $p<0,05$, the differences were considered statistically significant.

Results

Comparative characteristics of patients with infiltrative (IT) and fibro-cavernous (FCT) TB

In the comparative analysis, we included only the infiltrative and fibro-cavernous TB forms, since other forms of pulmonary TB in our study, along with FCT, were also the result of the process progression, and the identification of factors associated with these forms was not part of the research objectives.

The results of a comparative analysis of patients with infiltrative and fibro-cavernous tuberculosis are presented in Table 2.

When comparing age characteristics, a predominance of persons under 40 years of age was revealed in both groups. At the same time, the differences in the groups “under 40 years old” and “over 40 years old” were more pronounced in the IT group (63.7% and 36.3%, respectively), while in the FCT group this difference was less pronounced (52.8% and 47.2%, respectively).

Males also predominated in both groups, however, in the FCT group, there were 5 times more males than females (83.3% versus 16.7%, respectively); in the IT group, there were 1.5 times more males (60.2% versus 39.8%, respectively).

Table 2 Basic characteristics of patients with infiltrative (IT) and fibrous-cavernous tuberculosis (FCT)

Parameter	Infiltrative TB (n=113)	Fibrous-cavernous TB (n=36)	P
Demographics			
Age (years)			
Up to 40 years old	72 (63,7%)	19 (52,8%)	0,242
Over 40 years old	41 (36,3%)	17 (47,2%)	
Gender, n (%)			
Females	45 (39,8%)	6 (16,7 %)	0,066
Males	68 (60,2%)	30 (83,3 %)	
BMI, n (%)			
Normal	99 (87,6 %)	19 (52,8 %)	0,001
Deficient	14 (12,4 %)	17 (47,2 %)	
Residence, n (%)			
City	72 (63,7 %)	22 (61,1 %)	0,920
Suburb	41 (36,3 %)	14 (38,9 %)	
Socio-economic indicators			
Social status, n (%)			
In work	30 (26,5%)	6 (16,7%)	0,2269
Unemployed	83 (73,5%)	30 (83,3%)	
Income, n (%)			
Above the living wage (LW)	41 (36,3 %)	10 (27,8 %)	0,3482
Below the living wage (LW)	72 (63,7 %)	26 (72,2 %)	
TB contact			
Yes	23 (20,4%)	7 (19,4%)	0,920
No	90 (79,6%)	29 (80,6%)	
HIV status			
Positive	5 (4,4%)	3 (8,3%)	0,298
Negative	108 (95,6%)	33 (91,7%)	
Comorbidities			
Yes	42 (37,2%)	19 (52,8%)	0,2835
No	71 (62,8%)	17 (47,2%)	
TB characteristic			
Microscopy			
Positive	40 (35,4%)	19 (52,8 %)	0,063
Negative	73 (64,6 %)	17 (47,2 %)	
Drug sensitivity, n (%)			
Drug sensitive	19 (16,8%)	5 (13,9%)	0,680
Drug resistant (MDR and/or XDR)	94 (83,2%)	31 (86,1%)	
TB type, n (%)			
New case	67 (59,3 %)	7 (19,4 %)	<0,0001
Relapse	46 (40,7 %)	29 (80,6 %)	
Duration of current treatment, n (%)			
From 1 to 6 months	87 (77%)	22 (61,1%)	
From 6 to 12 months	20 (17,7%)	8 (22,2%)	
>1 year	6 (5,3%)	6 (16,7%)	
Results of specific production of antibodies to lipoglycan of MTB			
Positive	30 (26,5%)	29 (80,6%)	<0,0001
Negative	83 (73,5%)	7 (19,4%)	

The number of underweight individuals was significantly higher in the FCT group of compared to the IT group (47.2% and 12.4%, respectively, p=0,001).

There were no differences in the place of residence of IT patients and FCT patients (urban/rural). The unemployed predominated in both groups, while in the FCT group there were 5 times more unemployed (83.3% of the unemployed versus 16.7% of the employed), while in the IT group there were 2.7 times more unemployed (73% unemployed versus 26.5% employed). In terms of income, similar trends were observed. Individuals with incomes below the subsistence minimum predominated in both groups. The FCT group had 2.6 times more people with income below subsistence compared to people with incomes above the subsistence level (72.2% versus 26.8%), while in the IT group this difference was 1.7 times (63.7% versus 36.3%).

There were no differences in the presence of tuberculosis contact and HIV status in both groups. Concomitant diseases in the IT group were 1.7 times less compared to the absence of such (37.2% vs. 62.8%), while in the FCT group, comorbidities occurred in 52.8% of patients.

A positive microscopy result was found in 35.4% of IT patients, while in FCT patients a positive result was found in 52.8% of patients. There were no differences in the frequency of drug-resistant and drug-resistant forms in both groups. However, the recurrence of the disease occurred 2 times more

Table 3 Regression analysis by factors associated with fibrous-cavernous tuberculosis

№	Factors	Unadjusted OR	p	Adjusted OR	p
1	**Gender**				
	Females	reference	reference		
	Males	3,3088 (1,2745- 8,5902)	**0,010**	2.813 (0.935-8.462)	0.066
2	**Age**				
	Up to 40 years old	reference	reference		
	Over 40 years old	1.5712 (0.736- 3.3545)	0,241	1,454 (0,524-4,035)	0,472
3	**BMI**				
	Normal	reference	reference		
	Deficient	6,3271 (2,6746- 14,9673)	**<0,0001**	5,719(2,049-15,965)	**0,001**
4	**Comorbidities**				
	No	reference	reference		
	Yes	1,5125 (0,7092- 3,226)	0,283	1,358 (0,502-3,673)	0,547
5	**Microscopy**				
	Negative	reference	reference		
	Positive	2,0397 (0,9544- 4,3592)	0,063	1,170 (0,432-3,166)	0,758
6	**TB type**				
	New case	reference	reference		
	Relapse	6,0342 (2,4369- 14,9415)	**<0,0001**	3,374 (1,191-9,561)	**0,022**
7	**Duration of current treatment**				
	From 1 to 6 months	reference	reference		
	From 6 to 12 months	1,5818 (0,6155-4,0655)	0,337	1,789 (0,533-6,005)	0,347
	>1 year	3,9545 (1,1623- 13,4547)	**0,030**	4,413(0,927-21,009)	0,062
8	**Drug sensitivity**				
	Drug sensitive	reference	reference		
	Drug resistant (MDR and/or XDR)	1,2532 (0,4318- 3,6371)	0,680	1,070 (0,279-4,094)	0,922
9	**Results of specific production of antibodies to lipoglycan of MTB**				
	Positive	reference	reference		
	Negative	0,3576 (0,1544- 0,8284)	**0,014**	0,354 (0,126-0,995)	**0,049**

often in FCT patients compared with IT patients (80,6% vs. 40,7%, respectively, p<0,0001).

A positive result of specific production of antibodies to lipoglycan of MTB was found in 26,5% of IT patients, while in FCT patients a positive result was found in 80,6% of patients (p<0,0001).

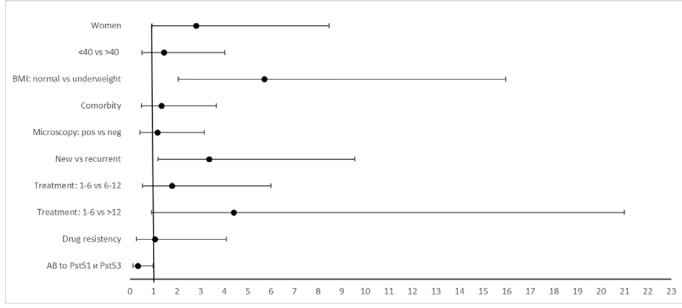
Factors associated with fibro-cavernous form of tuberculosis

The results of the regression analysis are presented in Table 3.

Binaric logistic regression with unadjusted odds ratio showed that male (OR=3.3088, 95% CI: 1.2745 - 8.5902, p=0.010), low BMI (OR=6.3271, 95% CI: 2.6746 - 14.9673, p<0.0001), TB recurrence (OR=6.0342, 95% CI: 2.4369 - 14.9415, p<0.0001), duration of treatment more than 12 months (OR 3.9545, CI: 1.1623-13.4547, p=0.014) were associated with FCT. At the same time, a negative result of specific production of antibodies to lipoglycan of MTB (OR=0.3576 95%, CI: 0.1544 - 0.8284, p=0.014) showed an inverse association with FCT.

We also tested the risk factors identified in the univariable model logistic regression in the multivariate regression model. Multivariate logistic regression analysis confirmed that low BMI (OR=5.719, 95% CI: 2.049–15.965, p=0.001), tuberculosis recurrence (OR=3.374, 95% CI: 1.191–9.561, p=0.022) were significantly associated with FCT. A negative result of specific production of antibodies to lipoglycan of MTB also showed an inverse association with PCT (OR=0.354, 95% CI: 0.126-0.995, p=0,049) (Figure 1).

Figure 1 -Adjusted odds ratio for fibrous-cavernous TB



Discussion

In our study, we found that male sex, low BMI, duration of treatment, recurrence, and increased production of anti-tuberculosis antibodies are factors associated with fibro-cavernous tuberculosis.

With regard to gender, it can be noted that, in general, the incidence of tuberculosis among men is significantly higher than among women, as evidenced by the ratio of men to women in case registration worldwide, equal to 1.7. It is assumed that both gender characteristics of behavior and biological factors associated with sex contribute to this [6].

At the same time, the predominance of men over women is observed in all TB forms.

In our study, multiple logistic regression analysis showed a 2.8-fold predominance of men in the group of FCT compared to women. However, significant differences were not found. The

data obtained by us are consistent with the data of other studies, which show that men are predisposed to such forms as fibro-cavernous, disseminated pulmonary tuberculosis, tuberculous pleurisy, and tuberculosis of the nervous system [7].

In regard to underweight, it can be noted that most studies indicate that low body mass index is a risk factor for active tuberculosis [8]. Moreover, nutritional imbalance can weaken the immune system and affect the outcome of TB treatment [9].

At the same time, the number of studies on the association of reduced weight with the development of fibro-cavernous tuberculosis is limited. Thus, Sun-Hyung Kim et al [5] obtained data similar to our results and showed that low BMI is associated with the risk of developing fibro-cavernous tuberculosis. The authors suggested that this may be due to activation of inflammatory processes. In particular, a reduced BMI has been shown to indicate the presence of nutritional deficiencies and is associated with increased lung inflammation and free neutrophil elastase activity in the lungs [10,11]. It has been suggested that this underlies the association between poor nutritional status and severe lung disease. At the same time, further research is needed to elucidate more precise mechanisms underlying the association between lower BMI and the FCT development. In our study, a low body mass index prevailed 5.7 times in FCT patients with a high level of significance of differences.

We also analyzed the association between the production of antibodies to secretory M. tuberculosis antigens and the FCT development [12].

Analysis of the antibodies production to lipoglycan of MTB antigens indirectly confirmed the hypothesis that in more severe TB forms, including FCT, there is an imbalance between Th1 and Th2 cells [13-16]. In particular, it was found that the cavities formation in TB patients is associated with the predominance of T-helper (Th)2 CD4+ cells in the alveoli [17] and the switching of the immune response to the synthesis of pro-inflammatory cytokines, such as IL-4, IL-5, IL-10 , IL-13. At the same time, switching to Th2 immune response is accompanied by an increase in antibody production [15], and therefore, it has been suggested that there are two types of tuberculosis, reflecting the ability of the immune system to control the antigen. The redirection of the immune response to certain IgG subtypes is accompanied by a decrease in the body's ability to fully eliminate M. tuberculosis. In our study, regression analysis showed that the probability of obtaining a positive result by immunochromatographic analysis of antibody detection in FCT is significantly higher compared to IT (p=0,049). Our data are consistent with the data of other authors, who also revealed an increased production of antibodies in fibro-cavernous tuberculosis [18]. At the same time, the causal relationship between the antibodies level and FCT has not yet been clearly established.

We also found association between the TB recurrence and the FCT. However, despite the fact that our results are consistent with those of Sun-Hyung Kim et al [5], we believe that this association is a reflection of the pathogenesis and course of FCT, which is characterized by a chronic course and a tendency to relapse, and thus, TB recurrence, can rather be considered as a consequence, rather than the cause, of the formation of the FCT.

Thus more studies are needed to clarify the causal association in FCT, both in relation to increased antibody production and the presence of TB recurrence.

We also found a treatment duration of more than 12 months to be almost 4.5 times more common in patients with fibro-cavernous tuberculosis, however, no significant differences were found. These data are also consistent with the data of other authors [5]. For example, it has been shown that refractoriness to treatment leads to the FCT formation [19].

Surprisingly, we did not find an association between the presence of comorbidities and FCT. At the same time, there is sufficient evidence that diabetes mellitus is a risk factor for fibro-cavernous tuberculosis [20,21]. We believe that the lack of association of comorbidities with FCT in our study is due to the fact that the majority of patients in our study group had multiple comorbidities. In this regard, it was not possible to single out a group with the presence of only diabetes mellitus or other concomitant disease. We believe that comorbidity with diseases with multidirectional pathogenesis had a leveling effect on the results of the analysis.

Conclusion

Weight deficiency, increased production of antibodies and disease recurrence are factors associated with fibro-cavernous tuberculosis.

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References

1. WHO. Global tuberculosis report. 2020:13.
2. Pavlunin A.V. Kavernoznyy i fibrozno-kavernoznyy tuberkulez legkikh: sovremennyy vzglyad na patogenez, diagnostiku i lechenie (Cavernous and fibrous-cavernous pulmonary tuberculosis: a modern view on pathogenesis, diagnosis and treatment) [Russian]. *STM*. 2012;1:115-122.
3. Urbanowski M.E., Ordonez A.A., Ruiz-Bedoya C.A., Jain P.S.K., Bishai W.P.R. Cavitary tuberculosis: the gateway of disease transmission. *Lancet Infect Dis.* 2020;20(6):e117-e118. https://doi.org/10.1016/S1473-3099(20)30148-1
4. Sarathy J.P., Zuccotto F., Hsinpin H., Sandberg L., Via L., Marriner G.A., et al Prediction of Drug Penetration in Tuberculosis Lesions. *ACS Infect. Dis.*2016;2:552–563. https://doi.org/10.1021/acsinfecdis.6b00051
5. Kim S.H., Shin Y.M., Yoo J.Y., Cho J.Y., Kang H., Lee H., et al Clinical Factors Associated with Cavitary Tuberculosis and Its Treatment Outcomes. *Journal of Personalized Medicine.* 2021;11:1-10. https://doi.org/10.3390/jpm11111081
6. Rhines A.S. The role of sex differences in the prevalence and transmission of tuberculosis. *Tuberculosis*. 2013;93(1):104-107. https://doi.org/10.1016/j.tube.2012.10.012
7. Moldobekova E.M. Gendernye osobennosti zabolevaemosti tuberkulezom v g.Bishkek (Gender characteristics of tuberculosis incidence in Bishkek) [Russian]. Ezhemesyachnyy nauchno-prakticheskiy meditsinskiy zhurnal «Meditsina Kyrgyzstana». 2013;4:207-210.
8. Badawi A., Gregg B., Vasileva D. Systematic analysis for the relationship between obesity and tuberculosis. *Public health.* 2020;186:246-256. https://doi.org/10.1016/j.puhe.2020.06.054

9. Yen Y.-F., Tung F.-I., Ho B.-L., Lai Y.-J. Underweight increases the risk of early death in tuberculosis patients. *Br J Nutr.* v 2017;118:1052–1060. https://doi.org/10.1017/S0007114517003166
10. Rytter M.J.H., Kolte L., Briend A., Friis H. Christensen, V.B. The Immune system in children with malnutrition—A Systematic review. PLoS ONE. 2014;9:E105017. https://doi.org/10.1371/journal.pone.0105017
11. Scrimshaw N.S., San Giovanni J.P. Synergism of nutrition, infection, and immunity: An overview. *Am. J. Clin. Nutr.*1997;66:464S–477S. https://doi.org/10.1093/ajcn/66.2.464S
12. Abilbayeva A.A., Tarabayeva A.S., Bitanova E.Zh., Erbolat D., Tuyebaeva B.T., Shuralev E.A. Effektivnost antigenov Mycobacterium tuberculosis v diagnostike tuberkuleza immunokhromatograficheskim ekspress-testom (The effectiveness of Mycobacterium tuberculosis antigens in the diagnosis of tuberculosis by immunochromatographic rapid test) [Russian]. *Vestnik KazNMU*. 2019;4:289-293.
13. Ashenafi S., Aderaye G., Bekele A., Zewdie M., Aseffa G., Hoang A.T. N., et al Progression of clinical tuberculosis is associated with a Th2 immune response signature in combination with elevated levels of SOCS3. *Clin Immunol.* 2014;151:84-99. https://doi.org/10.1016/j.clim.2014.01.010
14. Fan L., Xiao H., Mai G., Su B., Ernst J., Hu Zh. Impaired M. tuberculosis Antigen-Specific IFN-γ Response without IL-17 Enhancement in Patients with Severe Cavitary Pulmonary Tuberculosis. PLoS ONE. 2015;10(5):e0127087. https://doi.org/10.1371/journal.pone.0127087
15. Menon J., Hoeppner V. H., Judd A., Power C. A., Bretscher P. A. A hypothesis for the existence of two types of tuberculosis, reflecting two distinct types of immune failure to control the pathogen, based upon prevalence of mycobacterium-specific IgG subclasses. *Scand J Immunol.* 2018;87(6):e12665. https://doi.org/10.1111/sji.12665
16. 16. Wang L, Cai Y, Cheng Q, Hu Y, Xiao H Imbalance of Th1/Th2 cytokines in patients with pulmonary tuberculosis. *Chinese Journal of Tuberculosis and Respiratory.* 2002;25(9):535-537.
17. Mazzarella G., Bianco A., Perna F., D'Auria D., Grella E., Moscariello E., Sanduzzi A. T lymphocyte phenotypic profile in lung segments affected by cavitary and non-cavitary tuberculosis. *Clin. Exp. Immunol.* 2003;132:283–288. https://doi.org/10.1046/j.1365-2249.2003.02121.x
18. Sakamuri R.M., Ryndak M.B., Singh K.K., Laal S. Evolution of Antibodies to Epitopes of PE_PGRS51 in the Spectrum of Active Pulmonary Tuberculosis. *J Infect Dis.* 2020;221(9):1538–1541. https://doi.org/10.1093/infdis/jiz546
19. Porkulevich N.I., Mordyk A.V., Gurova Ya.V., Martynova G.G. Analiz prichin formirovaniya fibrozno-kavernoznogo tuberkuleza (Analysis of the causes of fibrous-cavernous tuberculosis formation) [Russian]. Tuberkulez i bolezni legkikh. 2015;5:154-155.
20. Chiang C.-Y., Lee J.-J., Chien S.-T., Enarson D.A., Chang Y.-C., Chen Y.-T., et al Glycemic control and radiographic manifestations of tuberculosis in diabetic patients. *PLoS ONE.* 2014;9:e93397. https://doi.org/10.1371/journal.pone.0093397
21. Nakamura A., Hagiwara E., Hamai J., Taguri M., Terauchi Y. Impact of underlying diabetes and presence of lung cavities on treatment outcomes in patients with pulmonary tuberculosis. *Diabet. Med.* 2014;31:707–713. https://doi.org/10.1111/dme.12414